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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,228	12/03/2001	Karen M. Lyons	22058-554	7961

7590 03/25/2004

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,228	LYONS ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *28-31 and 33-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/25/02; 3/13/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Notice to Comply

DETAILED ACTION

Election/Restrictions

This office action is in response to a response to a restriction requirement filed 1/26/04. Applicant's election without traverse of Group I (claims 1-27 and 32) in the amendment filed 1/26/04 is acknowledged. Claims 28-31 and 33-38 have been withdrawn as drawn to non-elected subject matter.

Information Disclosure Statement

An IDS filed 3/25/02 and an IDS filed 3/13/03 have been identified and the documents considered. The document identified as C23 on the IDS filed 3/13/03 has been considered but has been crossed out as a PCT search report does not constitute a document under 37 CFR 1.98. The signed and initialed PTO Form 1449s have been mailed with this action.

Specification

The abstract of the disclosure is objected to because in line 2, "comprises" should be singular. In line 3, there is no space between the word "a" and the word "BMP-3". Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because of the following informalities: there is a blank page following the second line on page 36 and a blank page following the first line on page 37 and the first line on page 38. It is not clear if there were text or tables on these pages that have been omitted or if this is an intentional blank. On page 3, line 6, the sentence is incomplete. On page 3, line the word "BMP-3" is misspelled as "B.M'P-3". On page 41, line 19, the word "BMP-2"

is misspelled as "BIvIP-2" and on page 42,line 3, a period is inserted prior to the word "Msx2". Appropriate correction is required.

The application contains sequence disclosures that are encompassed by the definition for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). Specifically, there are sequences contained on pages 20, line through page 21 line, page 21 line, page 21, line through page 22, line page 22 line, page 34 line through page 35, line and page 35. As well, there is a blank following the phrase "SEQ ID No" on page 8, line 12 indicating a SEQ ID NO should be inserted. However, the application fails to comply with the requirements of 37 C.F.R. 1.821(a)(1) and (a)(2) for the reasons set forth in the attached Notice to Comply With Requirements for Patent Applications Containing Nucleotide Sequence Disclosures And/Or Amino Acid Sequence Disclosures. If the sequences are listed in the sequence listing, it would be remedial to insert the appropriate SEQ ID Nos. If the sequences are not listed in the sequence listing, it would be remedial to file a substitute sequence listing, computer readable file and letter stating that the crf and paper sequence listing are the same and no new matter has been added and insert the appropriate SEQ ID Nos.

Applicants have indicated in an amendment filed 8/29/02 accompanied by a sequence disclosure that the specification has been amended to insert SEQ ID nos. However, an amendment to the specification has not been identified nor does the transmittal letter indicate the inclusion of such an amendment with the papers filed 8/29/02.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). See the signature page of Matthew Bahamonde in which the middle initial F has been changed to an E.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The invention recites a method for reducing the severity of bone fractures, reducing the incidence of a bone fracture and a method for treating osteoporosis in a subject by administration of an agent that inhibits BMP-3 activity or expression. The invention utilizes a combination of molecular biology and clinical techniques.

2) **Scope of the invention**. Applicants recite that an inhibiting agent can be anti-BMP-3 antibody or an anti-BMP-3 antisense RNA, which are administered to a subject therapeutically. The steps of gene and antibody therapy exacerbate a complex method.

3) **Number of working examples and guidance**. Applicants have generated a BMP-3 deficient mice to analyze BMP-3 function *in vivo*. These mice exhibited no skeletal deformities and increased bone density. Therefore, applicants propose that they have devised a treatment for reducing the severity of bone fractures, reducing the incidence of a bone fracture and a method for treating osteoporosis in which a subject is provided an agent that inhibits BMP-3 expression or activity. The specification discloses that an agent that inhibits BMP-3 activity can be an antibody or a receptor fragment of activin, a BMP-3 receptor. Agents with the potential to inhibit BMP-3 expression include anti-BMP-3 antisense molecules, ribozymes and peptide nucleic acids (PNA). The specification provides guidance for the technical aspect of generating any of these broad classification agents (pages 7, line 24 through page 26, line 14). Guidelines for pharmaceutically acceptable formulations, carriers and matrix are provided (see page 28, line 22 through page 30, line 8). Means of administration, dosage, formulations and regimens guidance is provided (pages 30, line 9 and pages 33, line 16). However, this guidance is general and broad. Applicants have provided no *in vitro* or *in vivo* experimental systems to

demonstrate or indicate that application of any specific inhibitor of BMP-3 expression or activity will result in said results.

4) **State of Art**. The application recites administration of antibodies to inhibit BMP-3 activity in a method that appears to require direct administration of the antibodies. The art of antibody therapy is an unpredictable art, which has been pursued for application to cancer treatment (see Halim, 1999). In this discipline, the right target, the right situation for treatment, the right mechanism and the right pairing of antibody and tumor type have eluded success (page 2, paragraph 5). Alternatively, the coding sequences of the antibodies can be administered as can the antisense molecules through gene therapy techniques. The art of gene therapy is also highly unpredictable. Three major obstacles for gene therapy are 1) gene expression 2) gene delivery and 3) efficacy and toxicity of administration (Meng and El-Diery, 1999). Vector based and non-vector based means of introducing the DNA into the cell to be expressed have not successfully overcome any of these obstacles.

The art of osteoporosis and osteoinduction treatment has typically been approached pharmaceutically with varied results (see page 2-3, Sambrook and Eisman, 2000). The use of gene therapy for the treatment of bone disease is being pursued as a potential application. However, the development of therapeutic targets is far from complete as is an understanding as to the exact nature of bone disease (see page 679, last three sentences, Cho and Nuttal, 2002). To date, therapeutic treatment of bone fractures and disease by antibody or gene therapy is highly unpredictable. The state of art of each goal alone is complex and requires great skill in the art.

BMP-3, bone-morphogenetic protein, is a major component of osteogenin. Functionally, BMP-3 has been shown to antagonize BMP-2 (see e.g. page 1, last paragraph), which mediates osteogenesis. Therefore, BMP-3 functions to inhibit bone growth.

5) **Unpredictability of the art**. The unpredictability of the invention is high due to the lack of recited *in vitro* and *in vivo* methods for the inhibition of BMP-3 activity and expression. Applicants disclose that transgenic mice deficient in BMP-3 exhibit reduced skeletal defects. However, neither antibody nor antisense agents are analyzed *in vivo* and *in vitro* for effects on bone fractures or osteoporosis. The unpredictability of using the claimed invention for use in humans is further mitigated due to the lack of methods or processes for gene therapy delivery of the agents of the instant invention. Many parameters must be addressed for *in vivo* use and yet there are no methods or means disclosed in the specification such as delivery methods for the introduction of the agents into humans, means of preparing the agents for *in vivo* applications, whether the DNA or protein is to be introduced and means of introduction, the right target, the right situation for treatment, the right mechanism and the right pairing of antibody and cell type. No *in vitro* or animal models have been provided as evidence of success of treatment.

6) Summary. The invention recites a method reducing severity of bone fractures, reducing the incidence of bone fractures and treating osteoporosis in a subject using inhibitors of BMP-3 activity and expression. In view of the unpredictability of the art to which the invention pertains and the lack of established protocols and the inability to predict what agents will function to inhibit BMP-3: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are

critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue, unpredictable experimentation in order to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 recites the limitation "said administration" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

March 15, 2004.

GERRY LEFFERS
PRIMARY EXAMINER